AMENDMENT

In the Claims:

Please amend the claims as follows:

43. (Amended) In combination, biologically effective amounts of:

(a) a first composition comprising at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;

(b) a second composition comprising a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and

(c) at least a second anti-cancer agent.

Please add claims 45-48 as follows:

-- 45. The combination of claim 43, wherein said first composition is a pharmaceutical composition.

46. The combination of claim 43, wherein said second composition is a pharmaceutical composition.

47. The combination of claim 43, wherein said at least a second anti-cancer agent is admixed with said at least a first targeting agent-therapeutic agent construct to form a therapeutic cocktail.

48. The combination of claim 43, wherein said at least a second anti-cancer agent is comprised within a composition distinct from said at least a first targeting agent-therapeutic agent construct. --.

RESPONSE

I. Status of the Claims

Prior to the present Action, claims 1-32, 43 and 44 were pending. According to a species election requirement, claims 1-9, 16-19, 24-32 and 43 read on the elected species and have been examined. Presently, claim 43 has amended to even further improve its clarity. No claims have been canceled. Claims 45-48 have been added, which read on the elected species and are fully supported by the original specification.

Claims 1-32, 43 and 44-48 are therefore in the case. For the convenience of the Examiner, a copy of the pending claims showing the present revisions is included herewith as **Exhibit A**. A clean copy of the pending claims is also included as **Exhibit B**.

II. Species Issues

The Action at page 2 states that claims 10-15, 20-23 and 44 "are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species" (emphasis added). Applicants respectfully point out that the rules governing the examination of species do not support the Action's position.

The Action's reference to 37 C.F.R. § 1.142(b) is misplaced as § 1.142(b) concerns restriction into independent and distinct inventions, *i.e.*, separate "Groups" of invention. In contrast, claims 10-15, 20-23 and 44 are only drawn to initially non-elected "species", the treatment of which is governed by 37 C.F.R. § 1.141(a). The pertinent rule provides that claims drawn to initially non-elected species are to remain pending in the case and are to be rejoined

upon allowance of a generic or linking claim. As the present response confirms allowability of the generic claims, the claims drawn to originally non-elected species must now be rejoined in the case. In any event, claims drawn to initially non-elected species always remain pending in the case and are not withdrawn from "further" consideration as alleged in the Action.

III. Support for the Claims

Support for the amended and newly added claims is to be found throughout the original specification as filed. Any fees necessary for the introduction of the new claims should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/3999.002383.

Elements (a) and (b) of claim 43 have each been clarified to recite that the targeting agent or detectable agent is comprised within a first or second composition, respectively. Support for this amendment is self-evident within the original claims and throughout the specification as filed. Particular written description support exists in specification at least at pages 37-44, with particular reference to page 37, line 29; page 38, line 6; page 42, last paragraph; and page 44, first and second paragraphs.

New claims 45 and 46 are supported by original claims 1 and 43 and have particular written description support in the specification, for example, at least at page 37, line 29 and at page 38, line 6.

Claims 47 and 48 are general counterparts to original claims 25 and 26. The admixture of anti-cancer agents to form therapeutic cocktails, as in claim 47, has exemplary support in the specification at least at page 44, first three paragraphs, with particular reference to lines 2, 3, 12, and 13.

It will therefore be understood that no new matter is included within the present amended and new claims.

IV. Summary

The present invention is generally directed to kits and combinations in which the essential biological component is a targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid. The present action at pages 3-8 includes various rejections based upon six different pieces of prior art, none of which mention aminophospholipids or targeting agents directed to aminophospholipids, let alone cancer treatment based upon any aspect of aminophospholipid biology. As aminophospholipids are completely absent from the cited references, which therefore clearly lack any meaningful teaching or suggestion, Applicants are perplexed that such rejections have been formulated.

Applicants respectfully invite consideration of the First Official Action issued in co-pending application Serial No. 09/351,457 ("the '457 application"; Attorney Docket No. 3999.002300), in which examination of method claims directed to aminophospholipid targeting and cancer treatment did not result in any rejections based upon prior art or double patenting **(Exhibit C)**. As the '457 application is based upon exactly the same specification as the present application, and as the method claims are directed to therapeutic intervention using targeting agent-therapeutic agent constructs that bind to aminophospholipids, examination of the '457 application is highly pertinent to the present case.

As examination of the '457 application did not lead to any rejections based upon prior art or issued patents, Applicants draw attention to the MPEP, which states that "the standards of patentability applied in the examination of claims must be the same throughout the Office" (MPEP at page 700-8, column 1). Indeed, MPEP 706 expressly states that "the examiner should never overlook the importance of his or her role in allowing claims which properly define the invention" (MPEP at page 700-8, column 1, paragraph 1). As all the art cited in the present case

is devoid of reference to aminophospholipids, and as counterpart method claims are free from rejection in the co-pending '457 application, Applicants respectfully submit that the present claims already properly define a patentable invention and that the double patenting and prior art rejections in this case are based on inadequate reasoning and should be withdrawn.

V. Rejection of All Examined Claims Under 35 U.S.C. § 112, Second Paragraph

The Action first rejects claims 1-9, 16-19, 24-32, and 43 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse.

As stated at page 3, the Action's concerns lie with the recitation of "biologically effective amounts". In the first instance, Applicants point out that it is the function of the specification, not the claims, to describe the invention. The Board of Patent Appeals and Interferences has clearly stated:

> "It is by now well established that it is the function of the descriptive portion of the specification and not that of the claims to set forth operable proportions and similar process parameters and that claims are not rendered indefinite by the absence of the recitation of such limitations."
>
> *Ex Parte Jackson*, 217 USPQ 804, 806 (P.T.O. Bd. App. 1982)

As recognized by the Examiner handling the co-pending '457 application, the common specification includes considerable details as to what constitutes "biologically effective amounts" in terms of the present invention. In particular, the specification explains that the effective amounts of the targeting agent-therapeutic agent constructs will be amounts effective to exert an anti-cancer effect, the specifics of which may vary according to the attached therapeutic agent. Exemplary therapeutic agents include anti-cellular, cytotoxic or anti-angiogenic agents and coagulation factors (specification at page 29, lines 13-16). The specification further teaches that

the therapeutic methods will "generally operate on the basis of the mode of action of the particular therapeutic agent or agents chosen for attachment to the targeting agent." As such, the use of cytotoxic agents will cause cellular destruction, whereas coagulants will act initially *via* coagulation (specification from page 12, line 28-page 13, line 7). Accordingly, the metes and bounds of the claim would be perfectly clear to one possessing an ordinary level of skill in the pertinent art in light of the particular application disclosure. *In re Moore*, 169 USPQ 236 (CCPA 1971).

Moreover, there is considerable case law concerning the acceptability of the exact term "effective amount". By way of example only, in *Ex Parte Skuballa*, 12 USPQ2d 1570 (B.P.A.I. 1989), the board reversed an examiner's rejection of claims that recited "an effective amount" after determining the phrase was definite in light of the disclosure. Claims 20 and 21 in that case were directed to inhibiting gastric secretions and achieving certain biological responses by administering "an effective amount" of a particular compound. The board found the phrase "an effective amount" to be definite.

Applicants further draw attention to *Application of Caldwell*, 319 Fed. 2d 254, 258 (C.C.P.A. 1963), holding that "'Effective amount' admirably states what is to be derived from the disclosure of the specification as to amount and we can see nothing 'critical' about the amount in determining the existence of patentable invention". Therefore, the case law indicates that the present claims are sufficiently definite in their recitation of effective amounts.

VI. Rejection of Claim 43 Under 35 U.S.C. § 112, Second Paragraph

Claim 43 is further rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to set forth the scope of the subject matter that the Applicants regard as their invention. Applicants respectfully traverse.

The Examiner particularly questions whether the claim adequately defines the inventive category that Applicants seek to protect (Action at page 3). The Action continues to set forth a number of questions, at one point inquiring whether the invention defined in claim 43 is "a method"? Applicants respectfully point out that as claim 43 does not include any method steps or verbs, it is evidently not a method claim.

Applicants further point out that this style of claim is completely acceptable under the law, and point to the recent issuance of claims in this format in the United States. By way of example, Applicants attach **Exhibit D**, which shows the issued claims in U.S. Patent No. 5,863,538 ("the '538 patent"; Attorney Docket Nos. 3999.000700; UTSD:452), all of which are drafted using the preamble "in combination". Although not at all necessary to support the patentability of claim 43, Applicants further point out that the '538 patent is incorporated by reference into the specification, for example, see at least page 31, line 24 and page 33, line 1.

Nonetheless, and without acquiescing with the present rejection in any way, claim 43 has been further optimized by incorporating the "comprising" language, as suggested in the Action at page 3, and in complete accordance with the claims issued in the '538 patent.

Each rejection under 35 U.S.C. § 112, second paragraph has therefore been overcome and should be withdrawn.

VII. Rejection of All Examined Claims for Double-Patenting

Claims 1-9, 16-19, 24-32, and 43 are further rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-49 of U.S. Patent No. 6,036,955 ("the '955 Patent"; Attorney Docket Nos. 3999.001700; UTSD:461) and claims 40-61 of U.S. Patent No. 6,051,230 ("the '230 patent"; Attorney Docket Nos. 3999.001000; UTSD:455). Applicants respectfully traverse.

The Action at page 4 alleges that the claims of the '955 and '230 patents overlap with those in the present application because all sets of claims are directed to "kits comprising a at least one [*sic*] targeting agent-therapeutic agent directed to an aminophospholipid, and at least a second targeting agent-therapeutic agent specific to coagulation of the tumor vasculature by delivery of a coagulant". This statement mischaracterizes the claims in each of the issued patents and those pending in the present application.

Aside from characterizing the claims in the '230 patent and the present application as requiring a second targeting agent that is linked to a coagulant, which is not a requirement of either set of claims, the most striking error in the Action's reasoning is that the claims of the '230 and '955 patents are directed to kits comprising a targeting agent-therapeutic agent construct that binds to an aminophospholipid. Applicants can find no reference to aminophospholipids in the claims of the cited patents. Should the present rejection be maintained, Applicants respectfully require the Office to point to the particular claims wherein the aminophospholipid terminology is believed to exist.

VIII. Rejection of All Examined Claims Under 35 U.S.C. § 103(a)

The Action next rejects each of the pending claims under 35 U.S.C. § 103(a) as allegedly being legally obvious the following separate combinations of references: Huang *et al.*, 1997, *Science*, 275:547-550, 1997 ("Huang") and Martin, U.S. Patent No. 6,043,094 ("Martin"); Gimbrone, U.S. Patent No. 5,632,991 ("Gimbrone") and Dvorak *et al.*, *Cancer Cells*, 3(3):77-85, 1991 ("Dvorak"); and the foregoing Gimbrone and Huang references. Applicants respectfully traverse each of the particular § 103 rejections.

A. Summary

In formulating the first of the § 103 rejections, the Action at the bottom of page 4 characterizes the instant claims as being directed to a "combination of a targeting agent-therapeutic agent construct, a targeting agent-detectable agent construct and at least a second anti-cancer agent". This is a mischaracterization of the claimed invention, which evidently leads to the errors in the various § 103 rejections advanced. It is also curious that this characterization of the invention conflicts with that in the immediate preceding paragraph at page 4 of the Action. The Action earlier assesses the present invention as being drawn to "kits comprising a at least one [*sic*] targeting agent-therapeutic agent directed to an aminophospholipid" (Action at the middle of page 4, emphasis added).

In beginning the analysis under § 103, the Action appears to have conveniently overlooked the fact that the present invention is fundamentally concerned with a targeting agent that binds to an aminophospholipid. As none of the cited references at all concern aminophospholipids, let alone the connection between aminophospholipids and cancer, tumor blood vessels or therapeutic conjugates, each of these rejections is based on entirely flawed reasoning. The rejections are thus *prima facie* improper and should be withdrawn.

The standard for legal obviousness stems from the Supreme Court's decision in *Graham v. John Deere Co.*, 148 USPQ 459 (U.S.S.Ct. 1966), in which court stated:

> "Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."
>
> 148 USPQ at 467 (citations omitted).

Applicants respectfully point out that the Office has not even reached the starting point for a proper *Graham v. John Deere* analysis. To follow the Supreme Court's analysis, one must have already construed the claimed invention correctly. In the present case, this has not been achieved, as the Action has interpreted the claims without reference to aminophospholipids. As such, the entire analysis of the scope and content of the prior art and the differences between the prior art and the claims at issue is improper. Applicants therefore respectfully request that the Office reconsider the entire issue of relevant prior art in light of the properly construed claims, which include a targeting agent-therapeutic agent directed to an aminophospholipid.

B. Huang and Martin

The Action at page 5 characterizes Huang as disclosing methods of occluding tumor vasculature using a bispecific antibody-tissue factor conjugate. The Action does not identify the component to which the bispecific antibody binds. Applicants point out that the bispecific antibody in question in fact binds to MHC Class II. MHC Class II is not an aminophospholipid. Applicants have studied the Huang reference and can find no discussion relevant to targeting aminophospholipids using bispecific antibodies. Should the Office maintain its position that Huang contains a teaching relevant to aminophospholipid targeting, Applicants respectfully invite the Office to point to the particular portions of the Huang reference that are believed to contain a relevant teaching.

The Action at page 5 continues to characterize Martin as disclosing liposome-based therapy in which the liposomes contain an affinity moiety that binds to a target surface at which the therapy is aimed. The Action particularly references Martin at columns 3, 13, 4, and 15. Applicants have studied the entire document, including the highlighted sections, and can find no

reference to aminophospholipids, let alone any suggestion of a targeting agent-therapeutic agent construct that binds to an aminophospholipid.

The only specific biological agent discussed in the Action is ELAM, which is not at all connected with aminophospholipids. Applicants further point out that the discussion in Martin at column 4, lines 1-5 is at odds with the present specification's teaching concerning the use of the claimed kits. In this context, Martin concerns the concept of inhibiting a pathogenic cell-binding event (Martin at column 3, line 61), whereas the present invention is concerned with delivering a therapeutic agent to aminophospholipids expressed on tumor vasculature. Therefore, Martin is not even in the same field of endeavor as the present invention.

Applicants further contest the Action's reasoning at page 6, and do not agree that Huang and Martin are combinable. However, as neither Huang nor Martin at all concern aminophospholipids, even if these references were combined, they still do not approach the standard required to support a proper rejection under 35 U.S.C. § 103.

C. Gimbrone and Dvorak

Gimbrone is characterized as disclosing a targeting agent conjugated to an antibody directed to ELAM-1 (Action at page 6). Even taking such an assessment at face value, Applicants are puzzled as to how such an anti-ELAM antibody could be held to be relevant to a targeting agent-therapeutic agent construct that binds to an aminophospholipid. Should the Office maintain that Gimbrone is relevant to such aminophospholipid targeting agents, Applicants respectfully request that the supposedly relevant portions of Gimbrone be specifically identified.

The Action bridging pages 6 and 7 interprets Dvorak as concerning "various strategies that would have possibly improved the delivery of monoclonal antibodies to tumor vasculature;

one of which is to identify the antigen that is uniquely expressed on tumor blood vessel endothelium". Again, the Action itself offers no reasoning to explain why Dvorak would be interpreted as relevant to targeting aminophospholipids. Should the Office believe that Dvorak contains a suggestion pertinent to aminophospholipid targeting, Applicants respectfully request that the apparently relevant suggestion be identified with particularity.

Although Dvorak's failure to provide any suggestion relevant to aminophospholipids is a striking flaw in the § 103 argument set forth, Applicants also respectfully point out that the Action has misinterpreted the general suggestion of Dvorak at pages 80-83. In particular, to the extent that Dvorak may be interpreted as suggesting targeting antigens "other than those associated with tumor cells" this document is still entirely directed to the desire to kill tumor cells directly. This is in marked contrast to the present invention, which is concerned with anti-cancer therapies based upon targeting tumor vasculature. The intent of Dvorak to attack tumor cells is particularly evident in the suggestion to link antibodies to α-particle emitting radioisotopes to "kill nearby tumor cells to which they have not physically attached" (Dvorak at page 83, column 2, last paragraph, emphasis added).

Considering the hypothetical combination of Gimbrone and Dvorak, as set forth in the Action at pages 7-8, Applicants again stress that the combination is entirely deficient as neither reference at all concerns aminophospholipid biology, aminophospholipids in the context of tumor blood vessels, or targeting agent-therapeutic agent constructs that bind to aminophospholipids. Should this rejection be maintained, Applicants respectfully request that the Office identify the precise suggestions that are believed to be relevant to the legal analysis under § 103.

D. Gimbrone and Huang

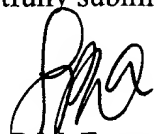
Finally, the Action at page 8 alleges that the combination of Gimbrone and Huang would render the present invention legally obvious under 35 U.S.C. § 103(a). This rejection is again advanced without any reference to aminophospholipids or targeting agents that bind to such components. Applicants incorporate by reference their reasoning in the foregoing sections, pointing to the deficiencies in the Gimbrone and Huang references. As outlined above, should the present rejection be maintained, Applicants most respectfully request that the sections of these documents supposedly relevant to aminophospholipids be identified more precisely.

In summary, none of the cited documents contain any suggestion of a targeting agent-therapeutic agent construct that binds to an aminophospholipid, let alone an adequate suggestion of such a construct in combination with a diagnostic or therapeutic agent designed for use in connection with cancer diagnosis or treatment. Accordingly, the present invention is clearly novel and non-obvious over the cited art and all rejections under § 103 should be withdrawn.

IX. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Sharareh have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,



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